DECLARATION OF DR. ANDREW R. BARRON

(37 C.F.R. § 1.132)

I, ANDREW R. BARRON, Ph.D. hereby declare and state as follows:

1. I received A.R.C.S. and B.Sc. (1st Class, Hones.) degrees, majoring in chemistry, at Imperial College of Science and Technology, University of London in 1986. I received a D.I.C. and Ph.D., specializing in inorganic chemistry at the same university in 1986. I was a Post-doctoral Research Associate, specializing in inorganic chemistry, at the University of Texas, Austin in 1986-1987.

2. I was an Assistant Professor and then an Associate Professor, specializing in inorganic chemistry, at Harvard University from 1987 to 1995.

3. In the fall of 1995, I went to Rice University, where I am currently the Charles W. Duncan, Jr. - Welch Chair of Chemistry and Professor of Materials Science in the Department of Chemistry and Department of Mechanical Engineering and Materials Science.

4. I have authored over two hundred journal articles and have made a like number of presentations.

5. I have been asked by the attorneys for the inventor Dr. A. Satyanarayan Naidu to use my technical expertise and consider an Office Action mailed January 12, 2004, in connection with the prosecution of U.S. Patent Appl. Ser. No. 09/980,062, filed on May 26, 2000 (the "Naidu application").

6. As part of my evaluation, I have studied the Naidu application and the Office Action, as well as all of the references cited in the Office Action.

The Immobilization of Lactoferrin

7. Lactoferrin (LF) has a bilboate structure, with a positively charged amino terminus (N-terminus) lobe and a negatively charged carbon terminus (C-terminus lobe). A full length LF peptide sequence has about 600 to about 800 continuous amino acids. Human LF in particular is about 703 amino acids long and has a molecular weight of about 83,000 Daltons.

8. The Naidu application describes LF immobilized on a naturally occurring substrate via its N-terminus region, *i.e.,* LF having its N-terminus region attached to a substrate leaving the C-terminus region free. (Naidu Appl. page 7, line 34-page 8, line 3.)

9. For the N-terminus region to become immobilized on a naturally occurring substrate, the region of the substrate to which the N-terminus region is to become attached should carry the opposite charge, *i.e.*, carry a negative charge.

US 6,475,511 B2

10. I have studied US 6,475,511 B2 by Gohlke and Cockrum ("Gohlke *et al.*"). Gohlke *et al.* describe compositions containing a combination of colostrum and lactoferrin in a "mucosal delivery format" ("MDF"). (Col. 6, lines 13-28.) The composition can also contain modified pectin. (Col. 6, lines 49-52.)

11. By MDF is meant a composition, such as a lozenge, formed of solid components. For example, Gohlke *et al.* teach, "The individual components of the composition may be obtained from commercial sources: colostrum (which is dehydrated by standard spray-drying procedures known in the art)" (col. 9, lines 41-44). Furthermore, examples 1 - 3 describe a process for preparing the product where, "[E]ach of the following ingredients is placed, in powdered form, into a commercial mixer." The ingredients are then mixed and cold pressed.

12. I have considered the examiner's suggestion that:

> "Gohlke *et al.* teach lactoferrin combined with colostrum . . . , pectin, and pharmaceutically acceptable carriers such as dextrose (see, *e.g.*, Examples 1-3). The components are thoroughly mixed and cold pressed to form a lozenge . . . Because the same components are present in the same compositions, inherently the lactoferrin in the lozenges of Gohlke *et al.* will be immobilized via its N-terminus to the proteins, polysaccharides, and lipids which are present to the same extent claimed by Applicant."

13. The mere presence of LF in a cold-pressed mixture with other solids, such as colostrum and modified pectin in an MDF format, would not inherently result in the LF becoming attached via its N-terminus.

14. Gohlke *et al.* do not disclose nor suggest any conditions under which the compounds could be mixed to result in the LF becoming attached via its N-terminus. For example, mixing LF with colostrum (and modified pectin) and cold pressing will not provide an

environment suitable to cause the LF to become attached to colostrums or modified pectin via LF's N-terminus region.

WO Patent Application 91/13982

15. I have studied WO Patent Application 91/13982 ("WO Patent Application '982"). This reference generally relates to human LF expressed using recombinant DNA. It discloses the use of this LF as a nutritional supplement, an antiseptic, and as a food-spoilage retardant. The LF can be compounded with certain carriers or diluents. It neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF.

16. I have considered the examiner's suggestion that:

> "The WO Patent Application '982 teaches LF in combination with stearic acid (which is a lipid and also corresponds to Applicant's pharmaceutically acceptable carrier of claim 102) or its salts . . . Because the same components are present in the same defined dispersion; inherently the LF in the composition of the WO Patent Application '982 will be immobilized via its N-terminus."

17. Stearic acid with a molecular weight of only 284.47 is not a substrate. LF could not become immobilized on such a small molecule. That would be akin to saying that a dog was immobilized on a flea, if a flea attached itself to a dog.

18. WO Patent Application '982 does not disclose nor suggest any other carriers or diluents that would be reactive with the N-terminus of LF and immobilize LF.

19. Furthermore, the mere presence in a mixture of LF and stearic acid or any of the other naturally occurring carriers or diluents taught in WO Patent Application '982 would not inherently result in the LF becoming attached via its N-terminus on a substrate.

20. WO Patent Application '982 does not disclose nor suggest any conditions under which the compounds could be mixed to result in the LF becoming attached via its N-terminus. Merely compounding solid LF with other solids, such as stearic acid, will not provide an

environment suitable to cause the LF to become attached to the other solid via LF's N-terminus region.

European Patent Application 753,309

21. I have studied European Patent Application 753,309 (European Patent Application '309). This reference generally relates to the preparation of mixtures of LF and desferrioxamine methanesulphonate useful for the therapy of viral infectious diseases. It neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF.

22. I have considered the examiner's suggestion that:

> "The European Patent Application '309 teaches compositions comprising LF and carriers such as paraffin oil and Vaseline (which are lipids), xantan gum and corn starch (which are polysaccharides), and lecithin (which is an emulsifier) . . . Because the same components are present in the same defined dispersion, inherently the LF in the composition of the European Patent Application '309 will be immobilized by its N-terminus . . ."

23. Paraffin oil and Vaseline are low molecular weight compounds, not substrates. LF could not become immobilized on such small molecules.

24. Paraffin oil and Vaseline do not have any reactive substituents or groups that would react with the N-terminus of LF. LF could not become immobilized on such inert molecules.

25. Furthermore, paraffin oil and Vaseline are hydrocarbons (not lipids) and do not carry any charge. As a result, neither paraffin oil nor Vaseline contains a region that will attach LF's positively charged N-terminus region.

26. Xantan gum and cornstarch do not carry any charges. As a result, neither xantan gum nor cornstarch contains a region that will attach LF's positively charged N-terminus region.

27. Lecithin is a low molecular weight compound. LF could not become immobilized on such a small molecule.

European Patent Application 753,308

28. I have studied European Patent Application 753,308 (European Patent Application '308). European Patent Application '308 generally relates to the use of LF for therapy of diseases caused by Gram-positive pathogen microorganisms. It neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF.

29. I have considered the examiner's suggestion that:

> "The European Patent Application '308 teaches compositions comprising LF and peppermint oil, gum base and corn starch (which are polysaccharides) . . . Because the same components are present in the same defined dispersion, inherently the LF in the composition of the European Patent Application '308 will be immobilized via its N-terminus . . ."

30. Peppermint oil is a low molecular weight compound, not a substrate. LF could not become immobilized on such a small molecule.

31. Peppermint oil, gum base and cornstarch do not carry any charges. As a result, neither gum base nor cornstarch contains a region that will attach LF's positively charged N-terminus region.

US Patent 6,066,469

32. I have studied US Patent 6,066,469 by Kruzel *et al.* ("Kruzel *et al.*"). This reference generally relates to LF expressed using recombinant DNA. It discloses the use of this LF as a nutritional supplement, an antiseptic, to treat and prevent opportunistic bacterial, viral and fungal infections, and as a food-spoilage retardant. It neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF.

33. I have considered the examiner's suggestion that:

> "Kruzel *et al.* teach nutritional supplements comprising LF in combination with adjuvants or diluents such as cellulose, starch,

tragacanth, and sodium carboxymethlycellulose . . . Because the same components are present in the same defined dispersion, inherently the LF in the nutritional supplements of Kruzel *et al* will be immobilized via its N-terminus . . ."

34. The mere presence in a mixture of LF and an adjuvant or a diluent, such as the solids cellulose, starch, tragacanth, and sodium carboxymethlycellulose would not inherently result in the LF becoming attached via its N-terminus.

35. Kruzel *et al.* does not disclose nor suggest any conditions under which the compounds could be mixed to result in the LF becoming attached via its N-terminus. Merely compounding solid LF with a solid adjuvant or a a diluent, such as cellulose, starch, tragacanth, and sodium carboxymethlycellulose will not provide an environment suitable to cause the LF to become attached to stearic acid via LF's N-terminus region.

36. Cellulose and starch do not carry any charges. As a result, neither cellulose nor starch contains a region that will attach LF's positively charged N-terminus region.

37. Furthermore, the mere presence in a mixture of LF and any of the adjuvants or diluents, such the solids cellulose, starch, tragacanth, or sodium carboxymethlycellulose would not inherently result in immobilization of the LF via its N-terminus.

38. Merely compounding LF with other solids, such as by cold-pressing two or more solids, will not provide an environment suitable to cause the LF to become immobilized via its N-terminus region.

I hereby declare that all of the statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I declare under the penalty of perjury, under the laws of the State of Texas, that the foregoing is true and correct.

Dated: July 26, 2004

Dr. Andrew R. Barron